Journal of Organometallic Chemistry 953 (2021) 122051

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

# A quick microwave preparation of isatin hydrazone schiff base conjugated organosilicon compounds: Exploration of their antibacterial, antifungal, and antioxidative potentials

Gurjaspreet Singh [a,*], Pooja Kalra [b], Akshpreet Singh [c], Geetika Sharma [a], Sanchita [a], Pawan [a], Mohit [a], Cristóbal Espinosa-Ruíz [d], María Angeles Esteban [d,**]

[a] Department of Chemistry and Centre for Advanced Studies, Panjab University, Chandigarh, 160014, India
[b] Department of Chemistry and Biochemistry, Sharda University, Greater Noida, 201310, Uttar Pradesh, India
[c] Department of Chemistry, DAV College, Sector 10, Chandigarh, India 160011
[d] Department of Cell Biology & Histology, Faculty of Biology, University of Murcia, 30100 Murcia, Spain

ARTICLE INFO

*Article history:*
Received 4 March 2021
Revised 5 August 2021
Accepted 18 August 2021
Available online 24 August 2021

*Keywords:*
Isatin hydrazone
Microwave synthesis
Antioxidant
Antibacterial
Antifungal

ABSTRACT

In the current study, five isatin hydrazone schiff base linked acetylinic scaffolds have been synthesized via condensation reaction of isatin hydrazone with aldehydic groups. In order to identify the structure characteristics of the prepared hydrazone derivatives, IR, $^{1}H$ and $^{13}C$ NMR spectroscopy, elemental analysis and X- ray crystallography were carried out. The antibacterial and antifungal activity of the derivatives against six bacterial strains (S. aureus, *S. Pyogenes*, E.coli, *V. cholera, L. monocytogens and H.influenza) and* seven fungal strains (*C. glabrata,C. parapsilosis, C. krusei, C. albicans, C. tropicalis, C. keyfer, and C. neoformans*) have been evaluated. All the compounds showed potent antibacterial activity with $IC_{50} \approx 7.81$ μM against *H. influenza* while the activity against fungal strains was less. Compounds a and c also had $IC_{50} \approx 7.81$ μM against *S. Pyogens.* Furthermore, the results of total antioxidant activity of hydrazone derivatives, expressed in terms of the ascorbic acid (mM) equivalents per mg of sample, indicates their superior bioactivity. These studies suggested that the istain hydrazone functionalized acetylenic derivatives could be an ideal biomaterial for antibacterial, antifungal and antioxidant applications. Besides this, these derivatives were transformed into isatin hydrazone appended 1,2,3 triazole based organotriethoxysilanes and their reaction conditions were optimised



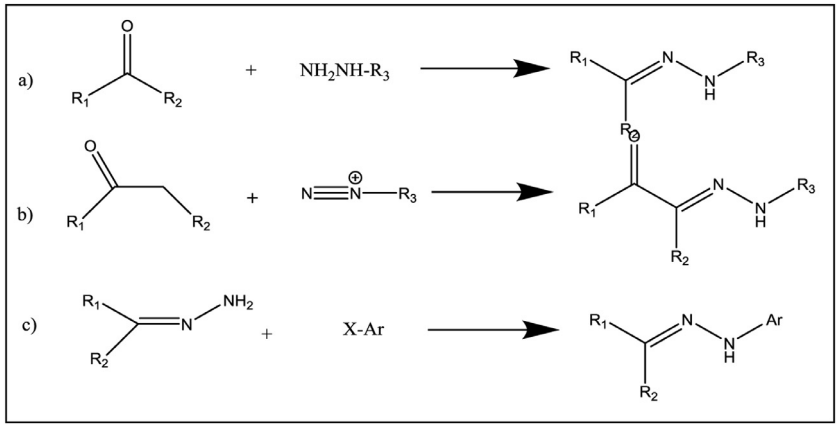
## 1. Introduction

The hydrazone scaffold is omnipresent in variety of fields starting from organic synthesis [1] and therapeutic chemistry [2] moving to supramolecular chemistry [3], dynamic combinatorial chemistry [4], hole-transporting materials [5], dye [6], metal-covalent organic frameworks [7], and among many other applications [8]. The use of hydrazones is very prominent and the reason being uncomplicated synthesis, compatibility, and ability to resist the hydrolysis. But the ground reality is uniqueness of azomethine group that aids its exploitation in numerous fields. An agile evaluation of the structure of a hydrazine discloses that it has (a) an imine carbon possessing both nucleophilic and electrophilic nature, (b) nucleophilic amino and imine kind of more reactive nitrogens, and (c) configurational isomerism curtails from the intrinsic nature of the C=N double bond.

These structural arrangements of atoms provide exclusive physical and chemical properties to hydrazones. Synthesis of hydrazones proceeds via three simple routes (Scheme 1), (i) condensation reaction between aldehydes or ketones and hydrazines [9,10] (ii) amalgamation between acids or $\beta$-keto esters and aryl diazonium salts that commonly referred as Japp–Klingemann reaction, [11] (iii) reaction between non-substituted hydrazones and aryl halides. [12,13]. Much attention has been given by the researchers in outlining the synthesis of novel hydrazones owing to the ease of synthetic procedure and structural flexibility. The resultant hydrazones are generally crystalline in nature and gets separated from the reaction mixture, which further ease their purification process and reinforce the exploitation of these entities. The hydrazones found to possess applications in numerous fields of chem-

* Corresponding author at: Department of Chemistry & Centre of Advanced Studies, Panjab University, Chandigarh, India.
** Co-corresponding author at: Department of Cell Biology & Histology, University of Murcia, 30100 Murcia, Spain.
*E-mail addresses:* gjpsingh@pu.ac.in (G. Singh), aesteban@um.es (M.A. Esteban).

https://doi.org/10.1016/j.jorganchem.2021.122051
0022-328X/




**Scheme 1.** The synthesis of hydrazones via (a) hydrazine–ketone/aldehyde condensation; (b) the Japp–Klingemann reaction; and (c) aryl halide substitution.

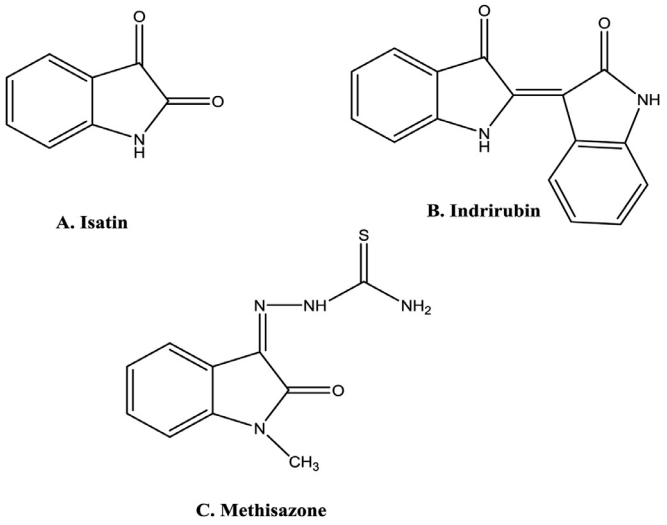



**Fig. 1.** Some of isatin derivatives containing bioactive molecules.

istry from synthetic chemistry [14] like preparation of compounds to analytical chemistry like detection of a large number of metal cations and the separation of carbonyl compounds [15]. Although, the most important property of hydrazones is, perhaps, their great pharmocophoric activity. In fact the physiological activity can be enhanced by coupling with other biological active moieties. Isatin (1H-indole-2,3-dione) regarded as a advanced range of heterocyclic moieties with many flattering actions and superior acceptance in human beings [16,17] was preferred as a biological active frame for coupling. The isatin derivatives SU-11248 (sunitinib) and SU-5416 (semaxanib) exhibits anti-angiogenic and tyrosine kinase inhibitory properties [18]. Schiff bases of isatins are described in literature and disclose broad range of antipathogenic properties, like antiviral [19], anti-mycobacterial [20], antitubercular [21], and antifungal [22].

However the upsurge in the activity against various pathogens provoked investigation of the structure activity relationships of 1H-indole-2,3-dionederivatives like 5-halogenation, N-Mannich base [23], N-alkylation [24], and 3-thiosemicarbazone. There are many drugs available in the market that posses 1H-indole-2,3-dione as an active scaffold. Two such examples are indirubin (Fig. 1B) and methisazone (Fig. 1C) [25-28].

Furthermore, the chemistry of 1,2,3-triazoles has established substantial interest due to their biological and synthetic significance [29]. Over the past few decades triazole loop is an impending biological unit that has been drastically endorsed [30]. Although 1,2,3-triazole moiety exist in nature, but there are many instances found in literature which depicts multifarious pharmacophoric properties linked to this scaffold, such as anti-HIV activity [31], antipathogenic activity [32], $\beta$-3-selective adrenergic agonism [33], kinase inhibitory [34] and other enzyme inhibitory activities [35]. However, one of the most important approach to design more active and new chemical species is molecular hybridization. This basically includes combination of two or more pharmacophoric unit into a single unit to enhance their activites [36]. So this approach was opted for the building of new pharmacophoric unit.

In fact, antioxidants play a major role in the mechanism to defend body by controlling the production and removal of the reactive oxygen species (ROS). The controlled mechanism includes removal of toxins of excess ROS, if not done then the high concentrations of free radicals can damage proteins, carbohydrates, lipids and normal cell structures and also destroys the nitrogen bases of nucleic acids which lead to certain transformations [37]. It also causes aging, cancer, neurodegenerative muddles such as Parkinson's and Alzheimer's diseases [38,39].

During the past two decades the world population is suffering brutally with the infectious diseases and among them, pathogenic infections are the second most leading death triggering diseases after heart attack in the world, due to their quick spreading rate, noxious nature and their ability to fight against the present antibiotic drugs. Considering this perspective, the preparation of pathogenic target based new antipathogenic agents has gained considerable attention in the drug discovery. This research is with an anticipation to find some new and more potent antimicrobial and antioxidant agents which competitively impedes side effects and enhanced effectiveness to heal pathogenic infections. The bioactivity results suggest the potential of these isatin hydrazone schiff base linked acetylinic scaffolds to be used as antimicrobial and antioxidant agents.

## 2. Experimental

### 2.1. Materials and methods

Chemicals such as substituted benzaldehydes (Avera), Propargyl bromide (Aldrich), Isatin (Loba Chemie), hydrazine hydrate (spectrochem), Bromotris(triphenylphosphine)copper(I) [$CuBr(PPh_3)_3$] (Aldrich), and potassium carbonate (Avera), were used as received. Solvents were dried and purified before use as per the conventional methods.

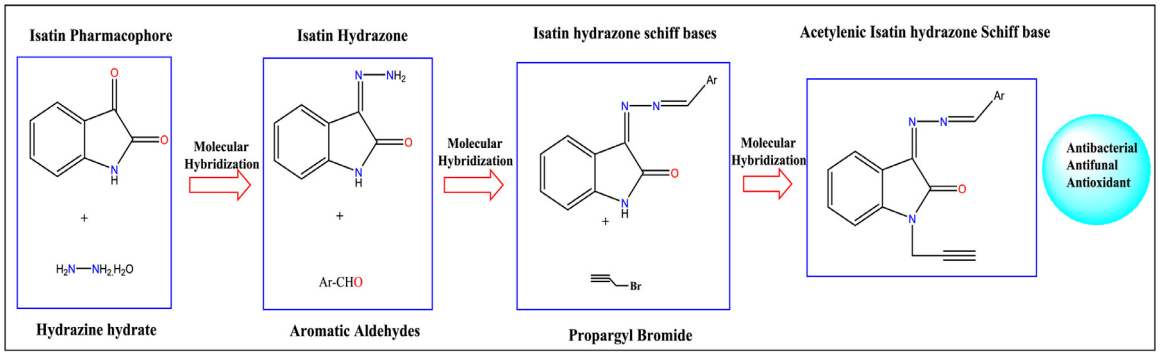



**Fig. 2.** Design approach of acteylenic isatin hydrazone Schiff base derivatives.

### 2.2. Instrument detail

The NMR spectra ($^1$H and $^{13}$C) were collected on a BRUKER (400 MHz) and JEOL (AL 300 MHz) spectrometer using $CDCl_3$ and DMSO-$d_6$/$CDCl_3$ solution as internal reference and chemical shifts were documented with respect to TMS. J values are reported in Hz. Infrared spectrum was obtained as Neat on a Thermo Scientific Fischer spectrometer. The synthesis was carried out on a Anton Paar Microwave PRO reaction system. Melting points were observed in a Mel Temp II device using sealed capillaries and are given as it is. Mass spectral measurements (ESI source with capillary voltage, 2500 V) were done on a VG Analytical (70-S) spectrometer. CHN examination was acquired on Perkin Elmer Model 2400 CHNS elemental analyzer.

## 3. Part 1 Synthetic route of acteylenic isatin hydrazone derivatives with various aromatic aldehydes

### 3.1. Strategy for design of library of acetylenic isatin hydrazones (Fig. 2)

### 3.2. General synthetic route for isatin hydrazones

First, isatin was made to react with hydrazine hydrate without any solvent. The molar ratio was kept 1:10. 1.0 equiv of isatin was dissolved in 10.0 equiv of hydrazine hydrate. This mixture was refluxed for 4 h and then filtered to get isatins hydrazones (IH). This mixture was irradiated with microwaves for 5 mins to obtained IH. Microwave synthesis outshines the tedious conventional synthesis.

### 3.3. General synthetic route for isatin hydrazone Schiff bases (IHSB) framework

Isatin hydrazone Schiff base compounds were synthesized viasingle pot reaction between synthesized IH with appropriate aromatic aldehydes following microwave as well as conventional methods (Scheme 2). Initially, isatin was made to react with variedly substituted aromatic aldehydes in ethanol. The mixture was heated till refluxing for 1.5 h and then filtered to get isatins hydrazone linked Schiff base (IHSB). Microwave method required time of 2-3 mins to obtained IHSB. The reaction showed selectivity and sensitivity towards the formation of desired products.

### 3.4. General synthetic route for acetylenic isatin hydrazone Schiff bases framework

A sample of **IHSB** (1 equiv) was mixed in 15ml of DMF, and dehydrated $K_2CO_3$ (1.5 equiv) was added to this solution. After the stirring for 30 min the reaction mixture was brought to 0 °C. To above mixture propargyl bromide (1.3 equiv) was sequentially added drop by drop. The reaction mixture was allowed to stir for 16 h at room temperature. The residue thus obtained was extracted withice cold water (50 ml) leading to the precipitates of acetylinic isatin hydrazone. Clear one spot for the product on TLC indicated the completion of reaction. The solid was dried to give a orange reddish products.

#### 3.4.1. Synthesis of (3Z)-3-(benzylidenehydrazono)-1-(prop-2-yn-1-yl)indolin-2-one ***(a)***

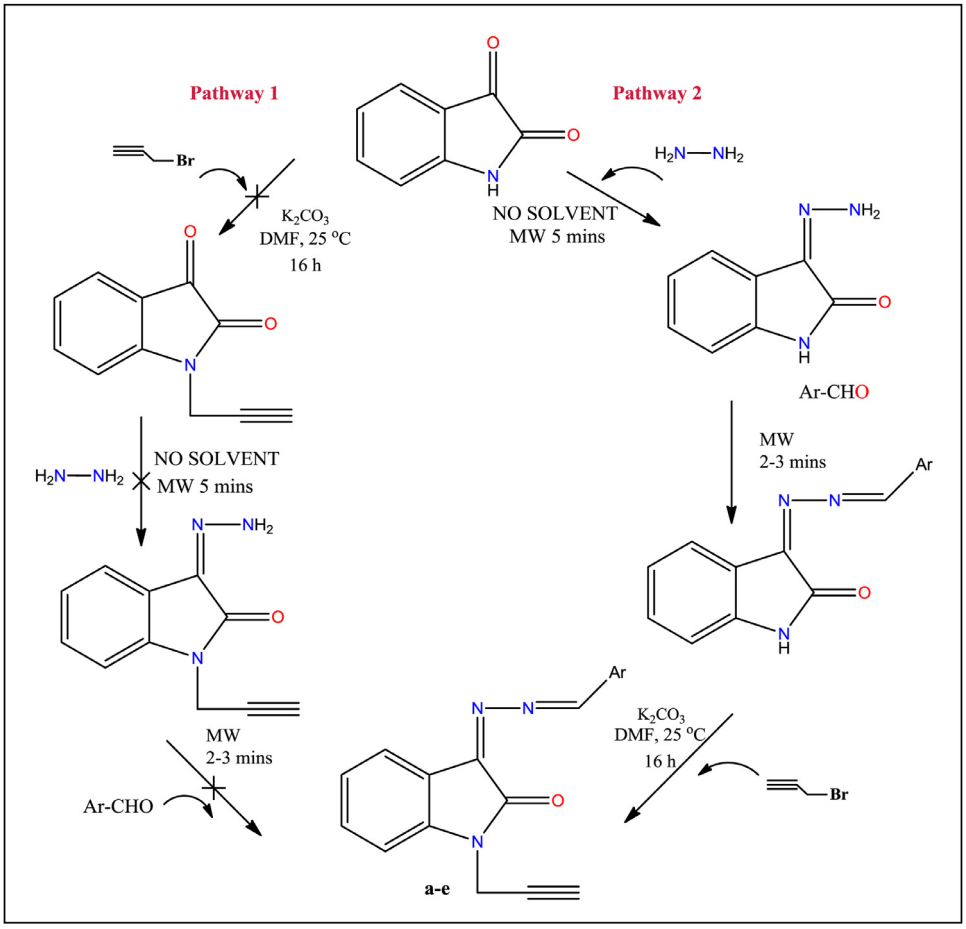
Red powder, Yield: 92%, M.P.: 64-66 °C. Anal. Calcd. for: $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.63. Found: C, 75.21; H, 4.59; N, 14.65. IR (neat, $cm^{-1}$): 1169 (N-$CH_2$),1613 (C=N), 1710 (C=O), 2121 (C≡C), 3276 (C≡C-H).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (s, 1H, -N=CH-), 8.21 (d, $J$ = 7.6 Hz, 1H, H4), 8.04 – 7.87 (m, 2H, H5, H9), 7.52 (dt, $J$ = 15.5, 6.7 Hz, 4H, H1, H3, H6, H7), 7.31 – 7.05 (m, 2H, H2, H8), 4.63 (d, $J$ = 2.6 Hz, 2H, -N-$CH_2$), 2.30 (t, $J$ = 2.6 Hz, 1H, -C≡CH). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 163.5 (s), 162.6 (s), 150.6 (s), 144.3 (s), 133.6 (s), 133.3 (s), 132.3 (s), 129.7 (s), 129.2 (s), 129.1 (s), 123.5 (s), 116.8 (s), 109.8 (s), 76.5 (s), 72.7 (s), 29.3 (s).

#### 3.4.2. Synthesis of (3Z)-3-((4-methoxybenzylidene)hydrazono)-1-(prop-2-yn-1-yl)indolin-2-one ***(b)***

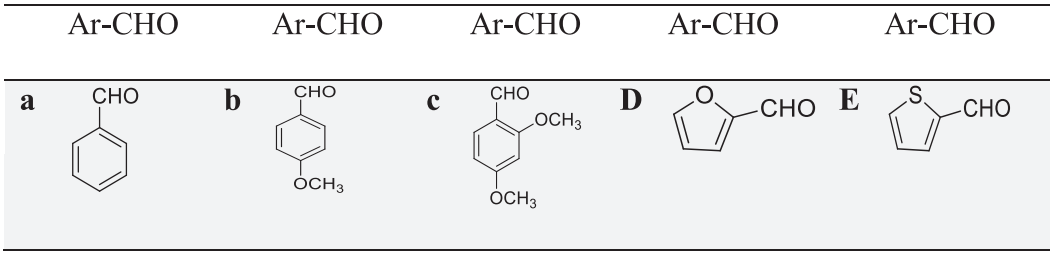
Orange powder, Yield: 93%, M.P.: 70-72 °C. Anal. Calcd. for: $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.90; H, 4.79; N, 13.25. IR (neat, $cm^{-1}$): 1178(N-$CH_2$), 1630 (C=N), 1714 (C=O), 2125 (C≡C), 3280 (C≡C-H).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.91 (s, 1H, -N=CH-), 8.70 (s, 1H, H5), 7.98 (d, $J$ = 7.5 Hz, 2H, H1, H2), 7.58 – 6.88 (m, 5H, H3, H4, H6, H7, H8), 4.62 (d, $J$ = 2.3 Hz, 2H, -N-$CH_2$), 3.92 (s, 3H, -$OCH_3$), 2.29 (t, $J$ = 11.9 Hz, 1H, -C≡CH). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 190.9 (s), 164.1 (s), 163.2 (s), 150.6 (s), 144.1 (s), 134.1 (s), 133.0 (s), 132.0 (s), 131.4 (s), 129.6 (s), 127.9 (s), 126.5 (s), 123.9 (s), 123.5 (s), 114.6 (s), 114.3 (s), 109.9 (s), 109.6 (s), 109.2 (s), 76.6 (s), 72.7 (s), 55.6 (s), 29.3 (s).

#### 3.4.3. Synthesis of (3Z)-3-((2,4-dimethoxybenzylidene)hydrazono)-1-(prop-2-yn-1-yl)indolin-2-one ***(c)***

Mustard powder, Yield: 84%, M.P.: 90-92 °C. Anal. Calcd. for: $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.15; H, 4.93; N, 12.10. IR (neat, $cm^{-1}$): 1185(N-$CH_2$), 1645 (C=N), 1719 (C=O), 2123 (C≡C), 3277 (C≡C-H). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.15 (s, 1H, -N=CH-), 8.34 (d, $J$ = 7.5 Hz, 1H, H5), 8.17 (d, $J$ = 8.7 Hz, 2H, H1, H4), 7.44 (t, $J$ = 8.3 Hz, 1H, H2), 7.20 – 7.00 (m, 1H, H3), 6.66 (d, $J$ = 8.7 Hz, 1H, H6), 6.49 (d, $J$ = 2.2 Hz, 1H, H7), 4.62 (d, $J$ = 2.4 Hz, 2H, -N-$CH_2$), 3.90 (s, 6H, -$OCH_3$), 2.28 (t, $J$ = 2.4 Hz, 1H, -C≡CH). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 164.9 (s), 163.9 (s), 161.7 (s), 161.3 (s), 150.2 (s), 143.9 (s), 132.7 (s), 129.8 (s), 129.5 (s), 123.3 (s), 117.2 (s), 115.6 (s), 109.5 (s), 106.4 (s), 98.1(s), 76.7 (s), 72.5 (s), 55.7 (s), 29.3 (s).




**Scheme 2.** Synthesis of acetylenic isatin linked hydrazones by microwave heating methods.




*3.4.4. Synthesis of (3Z)-3-((furan-2-ylmethylene)hydrazono)-1-(prop-2-yn-1-yl)indolin-2-one* ***(d)***

Mustard solid, Yield: 89%, M.P.: 64-66 °C. Anal. Calcd. for: $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.33; H, 4.05; N, 15.19. IR (neat, $cm^{-1}$): 1170(N-$CH_2$), 1680 (C=N), 1720(C=O), 2122 (C≡C), 3286 (C≡C-H). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.58 (s, 1H, -N=CH-), 7.75 – 7.40 (m, 2H, H1, H4), 7.13 (tt, $J$ = 20.4, 10.1 Hz, 4H, H2, H3, H5, H7), 6.65 (d, $J$ = 10.0 Hz, 1H, H6 $J$ = 2.4 Hz, 2H), 4.6 (d, $J$ = 2.4 Hz, 2H, -N-$CH_2$), 2.29 (t, $J$ = 2.4 Hz, 1H, -C≡CH). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 163.6 (s), 152.2 (s), 151.4 (s), 149.7 (s), 148.1 (s), 147.2 (s), 144.1 (s), 133.3 (s), 130.1 (s), 127.9 (s), 123.6 (s), 122.9 (s), 118.7 (s), 117.0 (s), 112.7 (s), 112.6 (s), 109.6 (s), 76.5 (s), 72.7 (s), 29.3 (s).

*3.4.5. Synthesis of (3Z)-1-(prop-2-yn-1-yl)-3-((thiophen-2-ylmethylene)hydrazono)indolin-2-one* ***(e)***

Dark red powered solid, Yield: 91%, M.P.: 74-76 °C. Anal. Calcd. for: $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32. Found: C, 65.50; H, 3.75; N, 14.39. IR (neat, $cm^{-1}$): 1177(N-$CH_2$), 1631 (C=N), 1710 (C=O), 2121 (C≡C), 3278 (C≡C-H). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.92 (s, 1H, -N=CH-), 8.34 (d, $J$ = 7.6 Hz, 1H, H1), 7.76 – 7.41 (m, 3H, H2, H3, H4), 7.17 (ddd, $J$ = 32.8, 16.9, 6.2 Hz, 3H, H5, H6, H7), 4.61 (d, $J$ = 2.4 Hz, 2H, -N-$CH_2$), 2.29 (t, $J$ = 2.4 Hz, 1H, -C≡CH). $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 163.7(s), 158.6 (s), 151.4 (s), 144.2 (s), 139.0 (s), 134.4 (s), 133.2 (s), 132.4 (s), 130.0 (s), 128.4 (s), 123.6 (s), 117.0 (s), 109.6 (s), 77.2 (s), 72.7 (s), 29.3 (s).

*3.5. X-Ray Crystallographic analyses*

The collection of the data was done on single crystals coated with Paratone-N oil and mounted on Kapton loops. X-ray data of all compounds were collected on a Bruker Kappa Apex II X-ray diffractometer ousted with a Mo X-ray source (sealed tube, $\lambda$ = 0.71073 Å) and an APEX II CCD detector equipped with an Oxford Cryosystems Desktop Cooler low temperature device. For data collection, cell refinement and reduction APEX-II soft-

**Table 1**
Selected crystal data and details on structure determinations from single crystal data for compounds **b** and **d**.

| Compound | B | D |
|---|---|---|
| Formula | $C_{19}H_{15}N_3O_2$ | $C_{16}H_{11}N_3O_2$ |
| MW [g·mol$^{-1}$] | 317.34 | 277.28 |
| Crystal system | Monoclinic | Orthorhombic |
| Space group | $P2_1/n$ | Pbca |
| a [Å] | 13.9951(14) | 11.7891(8) |
| b [Å] | 4.5504(5) | 14.2828(9) |
| c [Å] | 25.160(3) | 15.7846(9) |
| $\alpha$ [deg] | 90 | 90 |
| $\beta$ [deg] | 102.348(3) | 90 |
| $\gamma$ [deg] | 90 | 90 |
| V [Å$^3$] | 1565.2(3) | 2657.8(3) |
| T [K] | 170(2) | 170(2) |
| Z | 4 | 8 |
| $\rho_{calc}$ [g·cm$^{-3}$] | 1.347 | 1.386 |
| μ [mm$^{-1}$] | 0.090 | 0.095 |
| Min/max transmission | 0.992/0.999 | 0.985/0.995 |
| $\theta_{max}$ [deg] | 28.553 | 28.285 |
| Measured reflections | 44251 | 15691 |
| Unique reflections | 3966 | 3294 |
| Reflections [$F_0 > 4\sigma(F_0)$] | 1908 | 1597 |
| Parameter | 218 | 190 |
| $R_{int}$ | 0.1243 | 0.0953 |
| $R_1$ [$F_0 > 4\sigma(F_0)$] | 0.0604 | 0.0542 |
| $wR_2$ [all data] | 0.1563 | 0.1199 |
| GOF | 1.001 | 0.968 |
| □□$_{max}$/□□$_{min}$ [e·Å$^{-3}$] | -0.209/0.182 | -0.201/0.179 |
| CCDC number | 1554797 | 1554796 |

ware suite was used. [40]. Absorption corrections were applied using SADABS [41]. Space group assignments were done by examination of systematic absences, *E*-statistics, and successive refinement of the structures. Using intrinsic phasing methods implemented with ShelXT [42] structure solutions were performed and structure refinements were performed by least-squares refinements against $|F|^2$ followed by difference Fourier synthesis using ShelXL [43], both softwares are part of the ShelX [44] program package. Anisotropic displacement parameters were used to refine all non-hydrogen atoms. The C-H atoms were positioned with idealized geometry and were refined with fixed isotropic displacement parameters [$U_{eq}$(H) = -1.2·$U_{eq}$(C)] using a riding model with $d_{C\text{-}H}$ = 0.95 Å (aromatic) and 0.99 Å (methylene). CCDC- 1554797 (**b**) and 1554796 (**d**) contain the supplementary crystallographic data. These data can be gathered free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk. The detailed description of the crystallographic data and structure refinement parameters for compounds **b** and **d** are summarize in Table 1.

### 3.6. Crystal data

Single crystals were grown by slow evaporation of corresponding solutions in chloroform at room temperature for X-ray analysis confirmed the structural conformation of acetylinic isatin hydrazones **b** and **d** which crystallize in monoclinic $P2_1/n$ and orthorhombic *Pbca* space groups respectively, with all the atoms in the crystallographically independent general positions. The unit cell is composed of $a$ = 13.9951(4) Å, $b$ = 4.5504(5) Å, $c$ = 25.160(3) Å, $\beta$ = 102.34(3)°, V = 1565.2(3) Å$^3$, $\rho_{calc}$ = 1.347 g·cm$^{-3}$ for **b** and $a$ = 11.7891(8) Å, $b$ = 14.2828(9) Å, $c$ = 15.7846(9) Å, V = 2657.8(3) Å$^3$, $\rho_{calc}$ = 1.386 g·cm$^{-3}$ for **d**. ORTEP plots showing the asymmetric units are shown in Fig. 3 along with the atom labelling scheme.

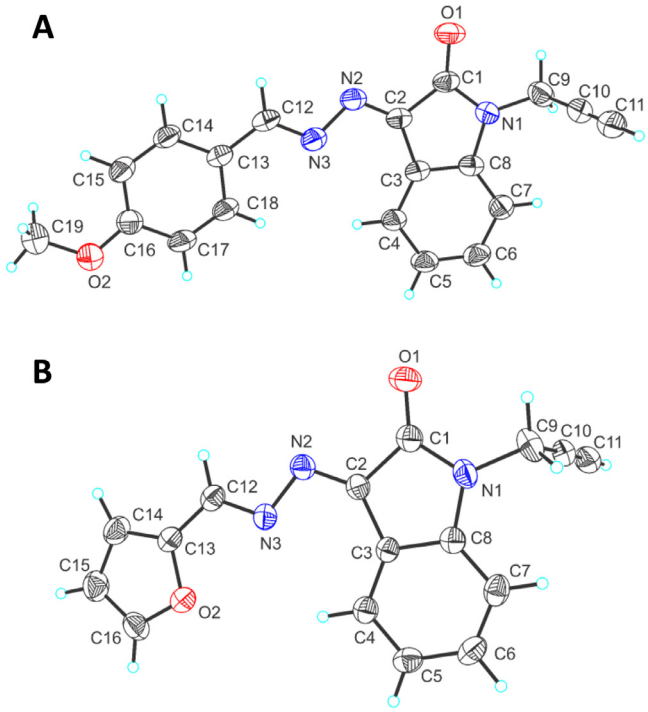



**Fig. 3.** ORTEP plots of acetylinic isatin hydrazones **b** and **d**

### 3.7. Biological assay

#### 3.7.1. Cell Culture

In order to investigate the microbial cells requiredwere obtained from Institute of Microbial Technology (MTCC-IMTECH) Chandigarh, Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh and National Collection of Pathogenic Fungi (NCPF)**.** The bacterial cells (*Staphylococcus aureus* MTCC3160, *Escherichia coli* MTCC2961, *Vibrio cholera* MTCC3906, *Enterococcus faecalis* MTCC 439, *L. Monocytogens*MTCC 839, *and Hemophillus influenza* MTCC 3826were cultured in MHB (Muller Hinton Broth, HiMedia, India). The fungal cells *Candida keyfer NPCPF 410004, Candida glabrata MTCC3019, Candida krusei NCPF 44002, Candida albicans NCPF 400034, Candida parapsilosis NCPF 450002, Cryptococcus neoformans* NCPF 250316 and *Candida tropicalis NPCPF420007* were made to grow in yeast extract-peptone-dextrose, HiMedia, India and Roswell Park Memorial Institute, HiMedia, Indiamedium. For agar plates, 2.5% (w/v) bacteriological agar (HiMedia, India) was added to the medium. The microbial cells were kept with 15% glycerol at -80 °C as frozen stock and were freshly revitalized on respective agar plates from the stock before each experimentation.

#### 3.7.2. In vitro Antibacterial activity

All the bacterial cells (*S. aureus, L. monocytogen, V. cholera, E. faecalis, H. influenza*, and *E. coli,*) were developed by keeping for the whole night and were diluted in MHB media to a cell density of $10^5$ CFU/mL. The Bacterial cells (100 μL) and compounds (250 - 0.112 μM) were made to dissolved in DMSO, and added into the 96-well flat bottomed microtiter plate (HiMedia, India). The plate was hatched at 37 °C for 24 hwithout shaking. visual and optical density was measured using a microtiter plate reader (BioRed, Model 680) at 600 nm. Kanamycin, a well-known antibacterial drug is used as a reference drug for the positive control. The Minimum inhibitory concentrations (MICs) was defined as the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.

**Table 2**
Antibacterial activity of the synthesized compounds.

| Compounds | Antibacterial Activity | | | | | |
|---|---|---|---|---|---|---|
| | *E. coli* | *S. aureus* | *S. pyogens* | *V. cholera* | *H. influenza* | *L. monocytogens* |
| A | >250 | >250 | **7.81** | >250 | **7.81** | >250 |
| B | >250 | >250 | **15.62** | >250 | **7.81** | >250 |
| C | >250 | >250 | **7.81** | >250 | **7.81** | >250 |
| D | >250 | >250 | **125** | >250 | **7.81** | >250 |
| E | >250 | >250 | **31.25** | >250 | **7.81** | >250 |
| Kanamycin | 3.90 | 31.25 | 31.25 | 62.50 | 62.50 | 125 |

It has been described in literature that macrocyclic compounds are potential candidates for suppressing microbial action so the favorable binding ability of the existing compounds stimulated us to examine the pharmacological action through antibacterial test. So the synthesized acetylenic isatin hydrazone derivatives **a-e** and kanamycin used as standard drug were investigated for their in vitro antibacterial assay for six bacterial strains *Staphylococcus aureus* (S. aureus), *Streptococcus pyogenes* (*S. Pyogenes*), Vibrio cholerae (*V. cholera*), Haemophilus influenzae (*H.influenza*), *Escherichia coli* (E.coli), and Listeria monocytogenes (*L. monocytogens)*.

The MIC of all assessed compounds are elaborated in Table 2. All the compounds investigated exhibits moderate to very good antibacterial efficiency. Particularly, compounds **a, b, c** depicted remarkable antibacterial efficiency to *H.influenza* and *S. Pyogenes.*

It is very exciting that the synthesized compounds have better antibacterial properties than the standard existing drug which can be attributed to the presence of different donor atoms such as nitrogen and oxygen in the molecules. Out of five synthesized compounds, **a** was found to inhibit the growth of bacterial strains strongly. Further, an increase in activity was observed on incorporation of methoxy group to unsubstituted isatin hydrazone nucleus. In addition, replacement of methoxy by di methoxy led to improved efficacy toward *S. pyogenes* and *H. influenza.* But still there is need to do more research to understand the effect of functional groups on bacterial proteins in order to identify the biological pathways

### 3.7.3. In vitro Antifungal activity

The antifungal assays of synthesized compounds **a-e** for fungal species (*C. glabrata, C. neoformans C. krusei, C. keyfer, C. albicans, C. tropicalis* and *C. parapsilosis*) were carried outas per the Clinical and Laboratory Standards Institute (CLSI) M27-A3 and M-38-A2 in RPMI 1640 medium by broth microdilution methods**.** The concentrations of all the compounds (**a-e**) varied between 250 μM and 0.110 μM. The 96 well flat bottom microtiter plates were incubated without shuddering at 30 °C for 48 h. The optical and visual density was calculated at 492 nm using a microtiter plate reader using BioRed, Model 680 for growth ninhibition. Amphotericin B, a known antifungal drug is used as a reference positive control.

Minimum inhibitory concentrations (MICs) ia defined as the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.

All the compounds (**a-e**) were also screened for their *in vitro* antifungal activity against *C. albicans, C. neoformans, C. krusei, C. keyfer, C. glabrata, C. tropicalis* and *C. parapsilosis*using positive control Amphotericin B. Evaluation of antifungal data (Table 3) revealed that, most of the evaluated compounds unveilednominal antifungal activity against all the tested microbial strains. Compared with the corresponding compounds, the compound **d** often display some unique properties such as improvement of biological activities including furan as a substituentwith MIC 15.62 μM. In addition to this, the compound **a** displayed nominal antifungal activity against *C. glabrata, C. parapsilosis,* and *C. tropicalis*with MIC of 31.25 μM. The SAR suggested that compounds with more electron withdrawing groups were found to be the most active against all tested fungi, and it was comparable to Amphotericin B.

### 3.8. Total antioxidant activity (TAA)

Using the method of Arnao, Cano and Acosta (1999), TAA was measured in particles.This method is based on the ability of the antioxidants in the sample to reduce the radical catión of 2,20-azino-bis-3-(ethylbenzothiazoline-6-sulphonic acid) (ABTS). This reduction was observed with the decolouration of $ABTS^{\cdot+}$, and measuring the quenching of the absorbance at 730 nm. A solution containing ABTS 2 mM, horseradish peroxidase 0.25 μM and $H_2O_2$ 35 μM was prepared. The particles were dissolved in PBS 50 mM pH= 7.5 and 50 μL of the suspension, containing 1 mg 100 $\mu L^{-1}$ was added to 950 μL of the ABTS solution. The change of absorbance was followed at 730 nm for five minutes. The determination of the activity was done by comparison of the values of the sample with a standard curve of ascorbic acid and expressed as ascorbic acid equivalents (mmol) per milligram of particle. All the samples reading were calculated thrice [45]. The Total antioxidant activity expressed in terms of equivalents of ascorbic acid (mM) per mg of nanoparticles (NP) as shown in Table 4.

A free radical is an unstable species with an unpaired electron. These free radicals can be stabilized by radical scavengers (ROS). In some of the cases, generation of ROS may surpass the antioxi-

**Table 3**
Antifungal activity of the synthesized compounds.

| Compounds | Antifungal Activity | | | | | | |
|---|---|---|---|---|---|---|---|
| | *C. kursei* | *C. albicans* | *C. tropicalis* | *C. parapolsis* | *C. kyfer* | *C. Glabrata* | *C. neoformans* |
| a | 31.25 | 125 | 31.25 | 31.25 | 125 | 62.50 | 125 |
| b | >250 | >250 | >250 | 62.50 | >250 | >250 | >250 |
| c | 62.50 | 125 | 125 | 125 | 62.50 | >250 | 62.50 |
| d | 15.62 | 62.50 | 125 | 62.50 | 125 | 125 | >250 |
| e | >250 | 62.50 | >250 | >250 | 125 | >250 | >250 |
| Amphotericin B | 0.78 | 0.78 | 0.78 | 0.78 | 0.78 | 0.78 | 0.39 |

**Table 4**
Total antioxidant activity expressed in equivalents of ascorbic acid (mM) per mg of nanoparticles (NP). (*n.d.* non detected).

| Sample Code | Taa (Eq.Asc) µm Mg Np |
|---|---|
| a | 14.3±2.6 |
| b | 3.4±0.5 |
| c | *n.d.* |
| d | 2.2±0.1 |
| e | *n.d.* |

dant mechanism of the cell, which leads to the damage of carbohydrates, cell proteins and lipids. The compounds which have ability to donate an electron to the free radical can stabilize the free radical and thereby helps in eradication of a number of biological disorders including nephrotoxicity, inflammatory process, cancer and liver damage. As a result of this it is very essential to synthesize the compounds bearing antioxidant activities. The data elucidates that synthesized compounds showed TAA values higher than the ascorbic acid (TAA = 1) which is a most important antioxidants. So their future aspects as antioxidants can be acknowledged. Results also depicted that, among the alkynes **a** is most efficient.

### 3.9. In silico pharmokinetic evaluation

The ADME properties of the prepared isatin hydrazone derivatives **a-e** were calculated using moleinspiration toolkit [46]. The gauged parameters are given in Table 2. Drug-likeness of the synthesized compounds compared with the known drugs was evaluated under Lipinski's rule. The synthesized compounds were evaluated for oral bioavailabilityon the basis oflogP (<5), MW (<500), HBA (≤10), and HBD (<5) values. Lipophilicity is predicted by logP in which P is the octanol-water partition coefficient. As depicted in the results all compounds have logP values within the defined unit. The number of rotatable bonds (nROTB) determines the molecular flexibility should be <10. All the compounds found to value in between 3–5. The topological polar surface area (TPSA) provides surface contribution of polar fragments. High TPSA values (>140 $Å^2$) is related to low blood-brain barrier (BBB) penetration, and poor membrane permeability. All the synthesized compounds are found to exhibit the TPSA values in the range of 17.30-37.53 Å2 (Table 2) which means evaluated compounds have good permeability in the cellular plasma membrane. The value of total number of hydrogen bond donors(HBD) should always be less than 5, and hydrogen bond acceptors (HBA) should be less than or equal to 10. All the compounds were found to have HBDs of and HBAs within the range. So, according to the Veber's rule [47] all compounds were expected to have good oral bioavailability and they were very well consistent with the ADME findings, no violations were expected for the synthesized compounds, affording positive drug-likeness values.

## 4. Part 2: Synthesis of Isatin hydrazone appended 1,2,3 triazole based organotriethoxysilanes

### 4.1. Traditional synthetic route for Isatin hydrazone appended 1,2,3 triazole organotriethoxysilanes

In a two neck round bottomed flask the Isatin hydrazone Schiff base acetylene (IHSBA) (1 equiv) was added to 1:1 THF/$Et_3N$ solvent mixture and the resulting mixture was stirred for at least 15 min at room temperature. Further AzPTES (1 equiv/alkyne function) and catalyst [$CuBr(PPh_3)_3$] (0.01 mmol/alkyne function) was added subsequently. The mixture was heated to 60 °C for 240 mins with continuous stirring. After 240 mins the heating was stopped and mixture brought to room temperature. The solvent were evaporated under vacuum with heating followed by slow addition of the hexane. The resulting mixture was filtered and concentrated under the reduced pressure to obtain colored silanes in high yield with good selectivity and sensitivity.

### 4.2. Microwave assisted synthetic route for 1,2,3 triazole organotriethoxysilanes

The microwave assisted route of synthesis includes one pot synthesis. This was done by irradiating the required acetylenic hydrazone with ϒ-azidopropyltriethoxysilane and [$CuBr(PPh_3)_3$] as a catalyst with microwaves (Scheme 3). The comparison between the microwave and conventional method for reaction time and yield in THF:TEA (1:1) was done in Table 6. The synthesis was done using Anton Paar monowave synthesizer-600®. This machine equipped with output power option ranging from 0 to 600W. It can supply continuous flow of microwave energy. All the synthesis process requires high quality borosilicate vial capped with a Teflon (PTFE) septum. At the extreme staring of the reaction temperature was attained till 100 °C. After this temperature vial with the reaction mixture was kept at the same temperature for 300 seconds. Lastly the reaction was brought to room temperature. The microwave synthetic route provides yield ranging between 82 to 95 % with reaction times of 5 min. However the conventional synthesis yield range from 71 to 89 %. This microwave route outweighs the conventional heating synthetic route.

#### 4.2.1. Synthesis of (3Z)-3-(benzylidenehydrazono)-1-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methyl)indolin-2-one ***(1a)***

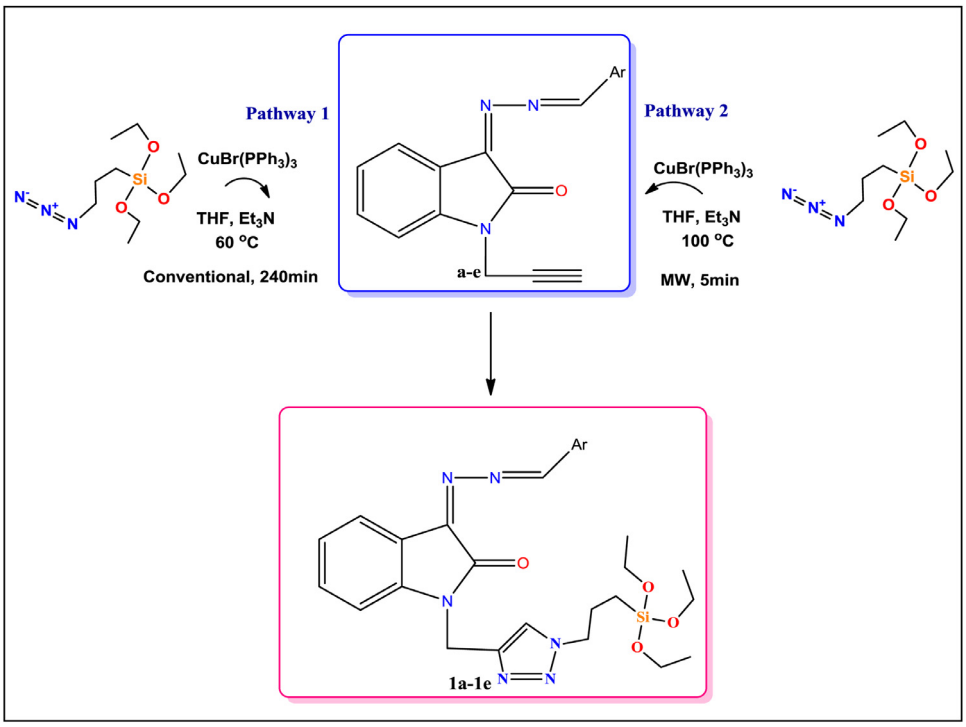
Red oil Yield: 94%, Anal. Calcd. for: $C_{27}H_{34}N_6O_4Si$: C, 60.65; H, 6.41; N, 15.72. Found: C, 60.61; H, 6.40; N, 15.79. IR (neat, $cm^{-1}$): 760, 1080 (Si-O), 952 (C-C), 1157(O-$CH_2$), 1247 (N-$CH_2$), 1255 ($CH_2$-N),1469 ($CH_3$-C), 1613 (C=N), 2968 (C=C-H).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (s, 1H, -N=CH-), 8.21 (d, $J$ = 7.6 Hz, 1H, H4), 8.04 – 7.87 (m, 2H, H5, H9), 7.52 (dt, $J$ = 15.5, 6.7 Hz, 5H, H1, H3, H6, H7, -Tz-H-), 7.31 – 7.05 (m, 2H, H2, H8), 5.35 (s, 2H, -$NCH_2$), 4.40 (t, $J$ = 7.2 Hz, 1H, -$N_3CH_2CH_2$), 3.82 (q, $J$ = 7.0 Hz, 6H, -$OCH_2CH_3$), 2.06 (dt, $J$ = 15.3, 7.5 Hz, 2H, $CCH_2$C-), 1.23 (t, $J$ = 7.0 Hz, 9H, $OCH_2CH_3$), 0.52(m, 1H, t, $J$ = 7.8 Hz, 2H, -Si**C**$H_2$-). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 158.1 (s), 153.2 (s), 142.5 (s), 138.4 (s), 134.3 (s), 126.2 (s), 123.0 (s), 120.8 (s), 120.5 (s), 113.2 (s), 62.7 (s), 58.5 (s), 52.7 (s), 24.3 (s), 18.2 (s), 7.4 (s).

#### 4.2.2. Synthesis of (3Z)-3-((4-methoxybenzylidene)hydrazono)-1-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methyl)indolin-2-one ***(1b)***

Orange oil Yield: 91%. Anal. Calcd. for: $C_{28}H_{36}N_6O_5Si$: C, 59.55; H, 6.43; N, 14.88. Found: C, 59.54; H, 6.39; N, 14.80. IR (neat, $cm^{-1}$): 765, 1078 (Si-O), 949 (C-C), 1158(O-$CH_2$), 1246 (N-$CH_2$), 1255 ($CH_2$-N),1479 ($CH_3$-C), 1630 (C=N), 2972 (C=C-H).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.12 (s, 1H, -N=CH-), 8.21 (d, $J$ = 51.7 Hz, 2H), 7.60 (s, 1H, -Tz-H-), 7.42 – 6.95 (m, 4H), 6.73 – 6.23 (m, 2H), 5.10 (s, 2H, -$NCH_2$-), 4.29 (t, $J$ = 7.3 Hz, 2H, -$N_3CH_2CH_2$), 3.90 (s, 3H, -$OCH_3$), 3.78 (q, $J$ = 7.1 Hz, 6H, -$OCH_2CH_3$), 1.98 (m, 2H, -$CCH_2$C-), 1.19 (t, $J$ = 7.0 Hz, 9H, $OCH_2CH_3$), 0.56 (t, $J$ = 7.8 Hz, 2H, -Si**C**$H_2$-). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 158.2(s), 153.1 (s), 143.7 (s), 137.4 (s), 134.3 (s), 126.31 (s), 122.3 (s), 120.8 (s), 120.5 (s), 113.2 (s), 62.5 (s), 58.7 (s), 55.3 (s), 51.5 (s), 25.3 (s), 18.2 (s), 7.4 (s).

#### 4.2.3. Synthesis of (3Z)-3-((2,4-dimethoxybenzylidene)hydrazono)-1-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methyl) indolin-2-one ***(1c)***

Dark yellowish oil, Yield: 89%. Anal. Calcd. for: $C_{29}H_{38}N_6O_6Si$: C, 58.57; H, 6.44; N, 14.13. Found: C, 58.54; H, 6.49; N, 14.10. IR (neat, $cm^{-1}$): 748, 1058 (Si-O), 954 (C-C), 1162 (O-$CH_2$), 1248 (N-$CH_2$),




**Scheme 3.** General synthetic procedure of isatin hydrazone triazole siloxy based scaffolds both via microwave as well as conventional heating method **1a-1e.**

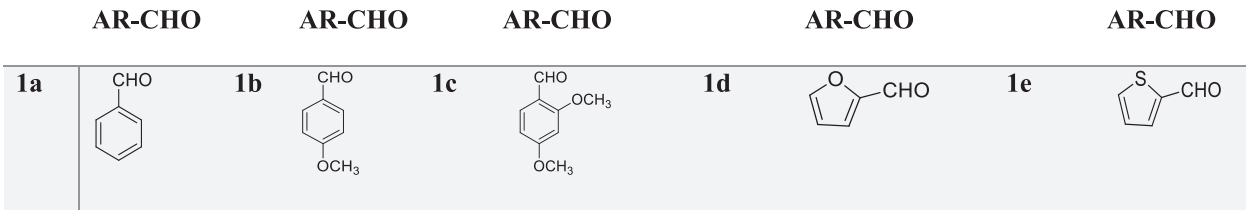



**Table 5**
Computational calculation of physicochemical pharmacokinetic parameters important for good oral bioavailability of synthesized compounds.

| Entry | TPSA | n-ROTB | MV | MW | mi logP | n-ON Acceptors | n-OHNH Donors | Lipinki's Violations | n atoms |
|---|---|---|---|---|---|---|---|---|---|
| Rule | - | - | - | ≤500 | ≤5 | ≤10 | ≤5 | ≤1 | - |
| A | 46.73 | 3 | 261.96 | 287.32 | 3.20 | 4 | 0 | 0 | 22 |
| B | 55.97 | 4 | 287.50 | 317.35 | 3.26 | 5 | 0 | 0 | 24 |
| C | 65.20 | 5 | 313.05 | 347.37 | 3.25 | 6 | 0 | 0 | 26 |
| D | 59.87 | 3 | 243.53 | 277.28 | 2.46 | 5 | 0 | 0 | 21 |
| E | 46.73 | 3 | 252.67 | 293.35 | 3.10 | 4 | 0 | 0 | 21 |

TPSA: topological polar surface area, n-ROTB: number of rotatable bonds, MV: molecular volume, MW: molecular weight, mi Log P: logarithm of partition coefficient of compound between n-octanol and water, n-ON acceptors: number of hydrogen bond acceptors, n-OHNH donors: number of hydrogen bonds donors.

**Table 6**
Optimisation of the reaction conditions of (**1a**)

| Entry | Solvent System | Time | Temperature | Yield | Heating System |
|---|---|---|---|---|---|
| 1. | THF:TEA (1:1) | 240 min | 60 °C | 85% | Oil Bath |
| 2. | THF:TEA (1:1) | 300 min | 50 °C | 78% | Oil Bath |
| 3. | THF:TEA (1:1) | 200 min | 70 °C | 80% | Oil Bath |
| 4. | THF:TEA (1:1) | 5 min | 100 °C | 98% | MW |
| 5. | THF:TEA (1:1) | 15 min | 60 °C | 92% | MW |
| **4** | THF:TEA (1:1) | 12 min | 70 °C | 89% | MW |

1252 ($CH_2$-N), 1462 ($CH_3$-C), 1633 (C=N), 2961 (C=C-H). $^1$HNMR (400 MHz, $CDCl_3$) $\delta$ 9.12 (s, 1H, -N=CH-), 8.21 (d, $J$ = 8.0 Hz, 2H, H1, H4), 7.60 (s, 1H, -Tz-H-), 7.40 – 6.93 (m, 3H, H2, H3, H7), 6.80 – 6.37 (m, 2H, H5, H6), 5.10 (s, 2H, -$NCH_2$-) 4.29 (t, $J$ = 7.2 Hz, 2H, -$N_3CH_2CH_2$), 3.89 (d, $J$ = 4.2 Hz, 6H, -$OCH_3$), 3.78 (q, $J$ = 7.1 Hz, 6H, -$OCH_2CH_3$), 1.98 (m, 2H, -$CCH_2$C-), 1.19 (t, $J$ = 7.1 Hz, 9H, -$OCH_2CH_3$), 0.66 – 0.49 (m, 2H, -Si**C**$H_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.7 (s), 157.4 (s), 152.6 (s), 146.3 (s), 136.9 (s), 133.7 (s), 132.8 (s), 131.9 (s), 129.8 (s), 128.5 (s), 126.2 (s), 123.3 (s), 115.5 (s), 114.2 (s), 62.5 (s), 58.4 (s), 55.4 (s), 52.4 (s), 24.0 (s), 18.2 (s), 7.3 (s).

#### *4.2.4. Synthesis of (3Z)-3-((furan-2-ylmethylene)hydrazono)-1-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methyl)indolin-2-one* ***(1d)***

Mustard oil, Yield: 91%. Anal. Calcd. for: $C_{25}H_{32}N_6O_5Si$: C, 57.23; H, 6.15; N, 16.02. Found: C, 57.24; H, 6.09; N, 16.03. IR (neat, $cm^{-1}$): 748, 1072 (Si-O), 949 (C-C), 1161(O-$CH_2$), 1246 (N-$CH_2$), 1261 ($CH_2$-N),1471 ($CH_3$-C), 1680 (C=N), 2962 (C=C-H).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.58 (s, 1H, -N=CH-), 8.36 (d, $J$ = 7.6 Hz, 1H, H1), 7.75 (s, 1H, -Tz-H-), 7.52 (d, $J$ = 15.6 Hz, 1H, H4), 7.23 – 6.50 (m, 5H, H2, H3, H5, H6, H7), 5.10 (s, 2H, -$NCH_2$-), 4.30 (t, $J$ = 7.2 Hz, 2H, -$N_3CH_2CH_2$), 3.78 (q, $J$ = 7.0 Hz, 6H, -$OCH_2CH_3$), 1.98 (q, $J$ =7.8 Hz, 2H, -$CCH_2$C-), 1.19 (t, $J$ = 7.0 Hz, 9H, -$OCH_2CH_3$), 0.64 – 0.44 (m, 2H, -Si**C**$H_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 163.5 (s), 159.6 (s), 152.2 (s), 142.9 (s), 141.3 (s), 128.6 (s), 122. 1(s), 113.9 (s), 107.3 (s), 100.1 (s), 62.3 (s), 58.7 (s), 52.7 (s), 24.4 (s), 18.1 (s), 7.6 (s).

#### *4.2.5. Synthesis of (3Z)-3-((thiophen-2-ylmethylene)hydrazono)-1-((1-(3-(triethoxysilyl)propyl)-1H-1,2,3-triazol-4-yl)methyl)indolin-2-one* ***(1e)***

Dark maroon oil, Yield: 89%. Anal. Calcd. for: $C_{25}H_{32}N_6O_4SSi$: C, 55.53; H, 5.97; N, 15.54. Found: C, 55.44; H, 5.99; N, 15.53. IR (neat, $cm^{-1}$): 749, 1068 (Si-O), 958 (C-C), 1150(O-$CH_2$), 1266 (N-$CH_2$), 1255 ($CH_2$-N),1439 ($CH_3$-C), 1630 (C=N), 2942 (C=C-H).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.92 (s, 1H, -N=CH-), 8.34 (d, $J$ = 7.6 Hz, 1H, H1), 7.76 – 7.41 (m, 4H, H2, H3, H4, -Tz-H-), 7.17 (d, $J$ = 16.9 Hz, 3H, H5, H6, H7), 5.10 (s, 2H, -$NCH_2$-), 4.30 (t, $J$ = 7.2 Hz, 2H, -$N_3CH_2CH_2$), 3.78 (q, $J$ = 7.0 Hz, 6H, -$OCH_2CH_3$), 1.98 (q, $J$ = 7.8 Hz, 2H, -$CCH_2$C-), 1.19 (t, $J$ = 7.0 Hz, 9H, -$OCH_2CH_3$), 0.64 – 0.44 (m, 2H, -Si**C**$H_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 168.35 (s), 146.9 (s), 129.3 (s), 125.1 (s), 122.1 (s), 121.1 (s), 120.3 (s), 113.2 (s),108.1 (s), 62.5 (s), 58.5 (s), 52.4 (s), 24.3 (s), 18.1 (s), 7.4 (s).

### *4.3. Spectroscopic analyses*

#### *4.3.1. IR spectra*

The vibrational spectroscopic data for all the newly synthesized compounds were recorded in the range of 4000-400 $cm^{-1}$. IR spectra of synthesized compounds bears a intense band at 1680 –1613 $cm^{-1}$ corresponding to $\nu$ (CH=N) that confirms the formation of imine bond. IHSB **a-e** show solid absorption bands in the region 1613-1680 $cm^{-1}$ and 1710-1722 $cm^{-1}$corresponding to C=N and C=O stretching vibrations respectively. The stretching vibrations bands of acetylinic isatins **a-e** in the region 2120-2125 $cm^{-1}$ and 3276-3286 $cm^{-1}$ attributes to the presence of C≡C and C≡C-H in alkyne functionality. The empty area around 2000 $cm^{-1}$and 3200 $cm^{-1}$ in organosilicon compounds **1a-1e** substantiatesthe formation of triazole units from acetylinic moieties. However, cycloaddition was confirmed with the stretching vibrations of –C=CH in triazole ring around 2942-2972 $cm^{-1}$. Furthermore, the stretching vibrations bands in the range of 745-765 $cm^{-1}$and 1058-1080 $cm^{-1}$in all the silanes confirms the formation of silyl moieties.

#### *4.3.2. NMR spectra*

$^1$H NMR spectra of isatin hydrazone schiff base conjugated silanes **1a-1e** exposed new trend in signals as illustrated in NMR study. A set of multiplets due to –$CH_2$ unit of propyl chain was found in all the silanes **1a-1e**. The –$NCH_2$ linked to 1,2,3-triazole heterocycle depicted at $\delta\sim$ 5.32–5.10 ppm. The cyclisation of alkynyl moiety into triazole unit was confirmed from a shift in peak from $\delta \sim$ 2.34-2.4 to $\delta \sim$ 7.52-7.7 ppm in **1a-1e.** The multiplets in the region of $\delta \sim$ 8.31–6.80 ppm depicted aromatic ring protons**.** In addition to this, the –$OCH_3$ protons appeared as singlet in the region $\delta \sim$ 3.91-3.80 ppm. However, propyl chain was not effected even after the changing the substituents at aromatic ring. The –CH=N- proton appears at most deshielded region $\delta \sim$ 9.12-8.66 ppm.

In $^{13}$C NMR spectra, for the compounds **1a-1e,** the most deshielded region around $\delta \sim$ 166.7-153.2 ppm was due to carbonyl carbon. The carbon with the imine bond appears in the region $\delta \sim$ 153.2-158.2 ppm. For triethoxysilanes **1a-1e**the methylene carbonattached to silicon atom –C–Si– appeared around $\delta \sim$ 7.5-7.3 ppm. The carbon of the acetylenic isatin moiety **a-e** appear in the range of $\delta \sim$ 72.0-76.8 ppm that shift around $\delta \sim$ 142.6- 100.2 ppm in triazole compounds **1a-1e**, that endorses the cyclisation of alkyne and azide functionality to triazole unit.

#### *4.3.3. Mass spectra*

The mass spectra of isatin hydrazone linked silanes derivatives coincide with the predictable structures and have effectively illustrated the respective molecular-ion peaks with the addition of $H^+$ ions. The purity of all the compounds was tested by the CHN analytical studies on all alkynes (**a-e**) and silanes (**1a-1e**) and mass spectral studies for silanes **1c.** Molecular ion signal at m/z 565.2 [M+2H$^+$] in the mass spectrum of compound **1c** was observed which confirms its structure [Molecular Mass: 562.74].

## 5. Conclusions

In this paper, isatin hydrazone Schiff base linked organosilicon compounds were synthesized following the click silylation route. The basic acteylinic isatin hydrazone Schiff bases were gauged for antioxidant, antibacterial and antifungal activities. It was found that all compounds were more active against bacterial strains as compared to the fungal strain. Further, compounds disclosed TAA values which are found to be higher than the main significant antioxidant, ascorbic acid (TAA = 1). Results also specified that among the alkynes, compound **a** is most efficient. *In silico* pharmokinetic evaluation of the compounds also gave positive drug-likeness values suggesting good oral bioavailability. Moreover, Isatin acteylinic isatin hydrazone were transformed into hydrazone Schiff base linked organosilicon compounds and their reaction conditions were optimized for both conventional and microwave heating method. The results of this article pave the way to extent the research of isatin moiety for producing more potent antimicrobial agents and antioxidants (Table 5).

## Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

## Acknowledgements

The authors would like to thank CSIR, New Delhi for providing necessary financial assistance.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2021.122051.

## References


[1] (a) M. Hidai, Y. Mizobe, Chem. Rev. 95 (1995) 1115–1133; (b) D. Enders, L. Wortmann, R. Peters, Acc. Chem. Res. 33 (2000) 157–169; (c) R. Lazny, A. Nodzewska, Chem. Rev. 110 (2010) 1386–1434; (d) S. Kobayashi, Y. Mori, J.S. Fossey, M.M. Salter, Chem. Rev. 111 (2011) 2626–2704; (e) T. Gebretsadik, Q. Yang, J. Wu, J. Tang, Coord. Chem. Rev (2020) 213666.

[2] (a) P. Vicini, F. Zani, P. Cozzini, I. Doytchinova, Eur.J. Med. Chem. 37 (2002) 553–564; (b) C. Loncle, J. Brunel, N. Vidal, M. Dherbomez, Y. Letourneux, Eur. J. Med. Chem. 39 (2004) 1067–1071; (c) L. Savini, L. Chiasserini, V. Travagli, C. Pellerano, E. Novellino, S. Cosentino, M. Pisano, Eur. J. Med. Chem. 39 (2004) 113–122; (d) M. Cocco, C. Congiu, V. Lilliu, V. Onnis, Bioorg. Med. Chem. 14 (2006) 366–372; (e) A. Masunari, L.C. Tavares, Bioorg. Med. Chem. 15 (2007) 4229–4236; (f) P. Vicini, M. Incerti, P.La Colla, R. Loddo, Eur. J. Med. Chem. 44 (2009) 1801–1807.

[3] (a) J.-M. Lehn, 2007 Chem. Soc. Rev., 36 151–160; (b) M. Barboiubook section Constitutional Dynamic Chemistry: Bridge from Supramolecular Chemistry to Adaptive Chemistry J.-M. Lehn, Topics in Current Chemistry, 322 Springer, Berlin, 2012, pp. 1–32. M. Barboiubook section Constitutional Dynamic Chemistry: Bridge from Supramolecular Chemistry to Adaptive Chemistry; (c) J.-M. Lehn, 2013 Angew. Chem., Int. Ed., 52 2836–2850.

[4] (a) S. Rowan, S. Cantrill, G. Cousins, J. Sanders, J. Stoddart, 2002 Angew. Chem.Int. Ed., 41 898–952; (b) P.T. Corbett, J. Leclaire, L. Vial, K.R. West, J.-L. Wietor, J.K.M. Sanders, S. Otto, 2006 Chem. Rev., 106 3652–3711; (c) B.L. Miller (Ed.), Bioorganic Chemistry, and Materials Science, Dynamic Combinatorial Chemistry, Drug DiscoveryJohn Wiley and Sons, Hoboken, New Jersey, 2010; (d) Y. Jin, C. Yu, R.J. Denman, W. Zhang, 2013 Chem. Soc. Rev., 42 6634–6654.

[5] R. Lygaitis, V. Getautis, J.V. Grazulevicius, Chem. Soc. Rev. 37 (2008) 770–788.

[6] R. Raue, A. Brack, K. Lange, Angew. Chem. Int. Ed. Engl. 30 (1991) 1643–1644.

[7] (a) F.J. Uribe-Romo, C.J. Doonan, H. Furukawa, K. Oisaki, O.M. Yaghi, J. Am. Chem. Soc. 133 (2011) 11478–11481; (b) D.N. Bunck, W.R. Dichtel, J. Am. Chem. Soc. 135 (2013) 14952–14955; (c) X.-P. Zhou, Y. Wu, D. Li, J. Am. Chem. Soc. 135 (2013) 16062–16065.

[8] (a) L. Popiotek, Biomed. Pharm. 141 (2021) 111851–111860; (b) B. Shao, I. Aprahamian, Chem. 6 (2020) 2162–2173.

[9] A.C. Day, M.C. Whiting, Org. Synth. 6 (1988) 10–12.

[10] G. Stork, J. Benaim, Org. Synth. 6 (1988) 242–244.

[11] (a) F.R. Jap, F. Klingemann, Ber. Dtsch. Chem. Ges. 20 (1887) 2942–2944; (b) F.R. Japp, F. Klingemann, Ber. Dtsch. Chem. Ges. 20 (1887) 3284–3286; (c) F.R. Japp, F. Klingemann, Ber. Dtsch. Chem. Ges. 20 (1887) 3398–3401; (d) F.R. Japp, F. Klingemann, Justus Liebigs Ann. Chem. 247 (1888) 190–225.

[12] S. Wagaw, B.H. Yang, S.L. Buchwald, J. Am. Chem. Soc. 120 (1998) 6621–6622.

[13] V. Lefebvre, T. Cailly, F. Fabis, S. Rault, J. Org. Chem. 75 (2010) 2730–2732.

[14] (a) Y.P. Kitaev, B.I. Buzykin, T.V. Troepolskaya, 1970 Russ. Chem. Rev., 39 441–456; (b) A.V. Xavier (Ed.), Frontiers in Bioinorganic Chemistry, VCH, 1985.

[15] (a) N.P. Du-Hoi, N.D. Xuong, N.H. Ham, F. Binon, R. Roger, J. Chem. Soc. (1953) 1358; (b) M. Fabin, G. Palmer, Biochemistry 40 (2001) 1867–1874.

[16] G. Singh, A.Singh Diksha, P. Satija, Mohit Pawan, D. González-Silvera, M.A. Esteban, New J. Chem. (2021), doi:10.1039/D1NJ00242B.

[17] H. Yakan, T.K. Bakır, M.S. Çavuş, and H. Muglu, 2020, 46, 5417-5440

[18] Med. Chem. 9 (2009) 397–414.

[19] J. Ma, S. Li, K. Reed, P. Guo, J.M. Gallo, J. Pharmacol. Exp. Ther. 305 (2003) 833–839.

[20] (a) D. Sriram, Y. Perumal, Curr. Med. Chem. 10 (2003) 1689–1695; (b) M.C. Pirrung, S.V. Pansare, K.Das Sarma, K.A. Keith, E.R. Kern, J. Med. Chem. 48 (2005) 3045–3050; (c) T.R. Bal, B. Anand, P. Yogeeswari, D. Sriram, Bioorg. Med. Chem. Lett. 15 (2005) 4451–4455.

[21] D. Sriram, P. Yogeeswari, G. Gopal, Eur. J. Med. Chem. 40 (2005) 1373–1376.

[22] L. Hua, W. Li, Y. Chen, K. Liang, H. Cai, J. Wang, S. Wang, T. Yin, L. Liang, Appl. Organomet. Chem. 35 (2021) 6081.

[23] S.N. Pandeya, D. Sriram, G. Nath, E. De Clercq, Arzneim. Forsch. Drug Res. 50 (2000) 55–59.

[24] M.T. Javid, F. Rahim, M. Taha, M. Nawaz, A. Wadood, M. Ali, A. Mosaddik, S.A. AliShah, R.K. Farooq, Bioorg. Chem. 79 (2018) 323–333.

[25] V.S. Velezheva, P.J. Brennan, V.Y. Marshakov, D.V. Gusev, I.N. Lisichkina, A.S. Peregudov, L.N. Tchernousova, T.G. Smirnova, S.N. Andreevskaya, A.E. Medvedev, J. Med. Chem. 47 (2004) 3455–3461.

[26] Z. Xiao, Y. Hao, B. Liu, L. Qian, Leuk. Lymphoma. 43 (2002) 1763–1768.

[27] D.J. Bauer, Antimicrob. Agents Chemother. 5 (1965) 544–547.

[28] M .C. Pirrung, S.V. Pansare, K.D. Sarma, K.A. Keith, E.R. Kern, J. Med. Chem. 48 (2005) 3045–3050.

[29] A. Rani, G. Singh, A. Singh, U. Maqbool, G. Kaur, J. Singh, RSC Adv. 10 (2020) 5610–5635.

[30] G Singh, P. Satija, A. Singh, Pawan Diksha, Sushma Suman, Mohit, S. Soni, Mater. Chem. Phys. 249 (2020) 123005.

[31] G. Singh, A. Singh, P. Satija, Mohit Shilpy, J.Singh Priyanka, A. Khosla, Inorg. Chim. Acta 514 (2021) 120028.

[32] G. Zoidis, E. Kritsi, P. Lecinska, M. Ivanov, P. Zoumpoulakis, M. Sokovic, M. Catto, Chem Med Chem 16 (2021) 134–144.

[33] L.L. Brockunier, E.R. Parmee, H.O. Ok, M.R. Candelore, M.A. Cascieri, L.F. Colwell, L. Deng, W.P. Feeney, M.J. Forrest, G.J. Hom, D.E. MacIntyre, L. Tota, M.J. Wyvratt, M.H. Fisher, A.E. Weber, Bioorg. Med. Chem. 10 (2000) 2111–2114.

[34] V. Pande, M.J. Ramos, Bioorg. Med. Chem. Lett. 15 (2005) 5129–5135.

[35] J. Shi, M. Ding, N. Luo, S. Wan, P. Li, J. Li, X. Bao, J. Agric. Food Chem. 68 (2020) 9613–9623.

[36] A. Nagarsenkar, S.K. Prajapti, S.D. Guggilapu, S. Birineni, S.S. Kotapalli, R. Ummanni, B.N. Babu, Med. Chem. Commun. 7 (2016) 646–653.

[37] G. Singh, A.Singh Diksha, G.Sharma Sanchita, Pawan Shilpy, C. Espinosa-Ruíz, M.A. Esteban, New J. Chem. 44 (2020) 6238–6250.

[38] T.J. Montine, K.S. Montine, W. McMahan, W.R. Markesbery, J.F. Quinn, J.D. Morrow, Antioxid. Redox Signal. 7 (2005) 269–275.

[39] J.A. Berliner, J.W. Heinecke, Free Radical Biol. Med. 20 (1996) 707–727.

[40] SAINT and APEX 2 Software for CCD Diffractometers, Bruker AXS Inc., Madison, WI, USA, 2014.

[41] G.M. Sheldrick, SADABS, version 2014/4, Bruker AXC Inc., Madison, WI, 2014.

[42] G.M. Sheldrick, Acta Crystallogr. A71 (2015) 3.

[43] G.M. Sheldrick, Acta Crystallogr. C71 (2015) 3.

[44] G.M. Sheldrick, Acta Crystallogr., Sect. A: Found. Crystallogr. A64 (2008) 112.

[45] MB Arnao, A Cano, M. Acosta, Free Radic Res 31 (1999) 389–396.

[46] http://www.molinspiration.com/

[47] D.F. Veber, S.R. Johnson, H.-Y. Cheng, B.R. Smith, K.W. Ward, J. Med.Chem. 45 (2002) 2615–2623.